

BEST CLINICAL PRACTICES

CHAPTER 13

from the

INTERNATIONAL POSITION PAPER

on

Women's Health and Menopause: A Comprehensive Approach

*National Heart, Lung, and Blood Institute
Office of Research on Women's Health
National Institutes of Health
and
Giovanni Lorenzini Medical Science Foundation*

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*NATIONAL HEART, LUNG,
AND BLOOD INSTITUTE*

*NIH OFFICE OF RESEARCH ON
WOMEN'S HEALTH*

*GIOVANNI LORENZINI MEDICAL
SCIENCE FOUNDATION*

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PREFACE

Women's health and menopause is a rapidly expanding field of medical practice and scientific investigation. It is a field of great social importance and impact, nationally and globally in developed as well as developing countries.

Menopause is a normal event in a woman's life. Some women view it as a positive and liberating experience. Others think of it as a negative event. Today, most women live long enough to become postmenopausal. In the developed world, the percentage of women over 50 years of age has tripled in the last 100 years. During this period, women's life expectancy in the United States has increased from 50 to 81.7 years, meaning that more than one-third of life will be lived in postmenopause.

This chapter on Best Clinical Practices summarizes the evidence-based recommendations from the International Position Paper on Women's Health and Menopause: A Comprehensive Approach, to be published by the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH) in the spring of 2002. The International Position Paper is based on extensive international review and evaluation of the scientific evidence for current clinical practices as presented in the published literature. The purpose of this international and multidisciplinary monograph is to enhance the composite health of menopausal and postmenopausal women on a global basis, and to make recommendations regarding needs for future research.

The International Position Paper represents the culmination of 7 years of cooperation between the NHLBI and the Giovanni Lorenzini Medical Science Foundation (Milan, Italy and Houston, TX, USA) in

a public/private partnership in the development and cosponsorship of four international conferences on Women's Health and Menopause since the mid-1990s. The first three conferences were held in Italy, and the most recent one in May 2001 in Washington, D.C. The last two conferences were also cosponsored by the NIH Office of Research on Women's Health. These conferences have addressed not only cardiovascular disease (CVD), but other health problems such as cancer, osteoporosis, and Alzheimer's disease, as well as the use and impact of hormone replacement therapy.

On behalf of the National Heart, Lung, and Blood Institute, I would like to thank Nanette K. Wenger, M.D., Chair of the Executive Committee of the International Position Paper; Rodolfo Paoletti, M.D., Cochair; Vivian W. Pinn, M.D., Cochair; the Panel Members; and the referees and reviewers for their valuable scientific contributions and dedication during this 4-year effort to critically review and evaluate extensive international databases on women's health and menopause. I hope that the readers will come away with a sense of appreciation for what biomedical research has accomplished in this important field and anticipation of the many opportunities and needs for future research.



Claude Lenfant, M.D.

Director, National Heart, Lung, and Blood Institute and Cochair, Executive Committee of the International Position Paper on Women's Health and Menopause: A Comprehensive Approach

INTERNATIONAL POSITION PAPER ON WOMEN'S HEALTH AND MENOPAUSE: A COMPREHENSIVE APPROACH

EXECUTIVE COMMITTEE AND PANEL

Nanette K. Wenger, M.D., USA served as the Chair of the Panel and Editor of the monograph. The Cochairs and Coeditors were Rodolfo Paoletti, M.D., Italy; Claude J.M. Lenfant, M.D., USA; and Vivian W. Pinn, M.D., USA

THE PANEL MEMBERS INCLUDED:

Elizabeth Barrett-Connor, M.D., USA
Martin H. Birkhäuser, M.D., Switzerland
Louise A. Brinton, Ph.D., USA
Aila Collins, Ph.D., Sweden
Peter Collins, M.D., UK
Pier Giorgio Crosignani, M.D., Italy
Lorraine Dennerstein, A.O., M.B.B.S., Ph.D.,
D.P.M., FRANZCP, Australia
Bruce Ettinger, M.D., USA
Jan-Åke Gustafsson, M.D., Ph.D., Sweden
Victor W. Henderson, M.D., M.S., USA

Susan Hendrix, D.O., USA
Carlo LaVecchia, M.D., Italy
Robert Lindsay, Ph.D., USA
Adriana Maggi, Ph.D., Italy
Joan A. McGowan, Ph.D., USA
Anne McTiernan, M.D., Ph.D., USA
Maryann Redford, D.D.S., M.P.H., USA
Susan M. Resnick, Ph.D., USA
Jacques E. Rossouw, M.D., USA
Sherry Sherman, Ph.D., USA

NONPANEL COAUTHORS

Additional authors who were invited to contribute to individual chapters:

Janet R. Guthrie, Ph.D., Australia
Barbara E.K. Klein, M.D., M.P.H, USA

Stefan Nilsson, Dr. Med. Sci., Sweden
Nanette Santoro, M.D., USA

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THE EXPERTS WHO REVIEWED THE PRELIMINARY INDIVIDUAL CHAPTERS INCLUDED:

Beth Alder, Ph.D., UK	Bert O'Malley, M.D., USA
Gloria A. Bachmann, M.D., USA	Bent Ottesen, M.D., Denmark
Linda Cardozo, M.D., UK	David Purdie, M.D., UK
Sir Richard Doll, UK	Lawrence G. Raisz, M.D., USA
Timothy M.M. Farley, Ph.D., Switzerland	Henri Rochefort, M.D., Ph.D., France
Marcha Flint, Ph.D., USA	Giuseppe Rosano, M.D., Ph.D., Italy
Silvia Franceschi, M.D., France	Raymond Rosen, Ph.D., USA
Ulysses J. Gaspard, M.D., Ph.D., Belgium	Karin Schenk-Gustafsson, M.D., Ph.D., Sweden
Anna Glasier, M.D., Ph.D., UK	Peter Schmidt, M.D., USA
Elina Hemminki, M.D., Ph.D., Finland	Ethel Siris, M.D., USA
Myra S. Hunter, Ph.D., UK	Sven O, Skouby, M.D., Denmark
Won-Whe Kim, M.D., Korea	Leon Speroff, M.D., USA
Britt-Marie Landgren, M.D., Ph.D., Sweden	John C. Stevenson, M.B.B.S., UK
Lenore Manderson, Ph.D., Australia	David W. Sturdee, M.D., UK
Olav Meirik, M.D., Ph.D., Chile	Cornelia Van Duijn, M.D., The Netherlands
Daniel R. Mishell Jr., M.D., USA	Nancy Woods, Ph.D., R.N., USA

THE EXPERTS WHO REVIEWED THE PRELIMINARY COMPOSITE DOCUMENT WERE:

Takeshi Aso, M.D., Ph.D., Japan	Michael Mendelsohn, M.D., USA
Giuseppe Benagiano, M.D., Italy	Henri Rozenbaum, M.D., France
Henry Burger, M.D., Ph.D., Australia	Goran Samsioe, M.D., Sweden
Desmond Julian, M.D., UK	Isaac Schiff, M.D., USA
Peter Kenemans, M.D., Ph.D., The Netherlands	Piero Sismondi, M.D., Ph.D., Italy
Luella Klein, M.D., USA	Wulf H. Utian, M.D., USA
Rogério Lobo, M.D., USA	Nelson Watts, M.D., USA

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CHAPTER 13 FROM THE INTERNATIONAL POSITION PAPER ON WOMEN'S HEALTH AND MENOPAUSE: A COMPREHENSIVE APPROACH

Elizabeth Barrett-Connor, M.D.; Susan Hendrix, D.O.**; Bruce Ettinger, M.D.****

Nanette K. Wenger, M.D. Chair; Rodolfo Paoletti, M.D., Cochair; Claude J.M. Lenfant, M.D., Cochair; Vivian W. Pinn, M.D., Cochair

Panel: Martin H. Birkhäuser, M.D.; Louise A. Brinton, Ph.D.; Aila Collins, Ph.D.; Peter Collins, M.D.; Pier Giorgio Crosignani, M.D.; Lorraine Dennerstein, A.O., M.B.B.S., Ph.D., D.P.M., FRANZCP; Jan-Åke Gustafsson, M.D., Ph.D.; Victor W. Henderson, M.D., M.S.; Carlo La Vecchia, M.D.; Robert Lindsay, Ph.D.; Adriana Maggi, Ph.D.; Joan A. McGowan, Ph.D.; Anne McTiernan, M.D., Ph.D.; Maryann Redford, D.D.S., M.P.H.; Susan M. Resnick, Ph.D.; Jacques E. Rossouw, M.D.; Sherry Sherman, Ph.D.

1. INTRODUCTION

The proportion of women living past the age of menopause has tripled during the past century, and is expected to increase steadily in the foreseeable future. If adulthood is defined as beginning at age 21, the average age at menopause as age 51, and the average life expectancy as age 81, women in the United States, in Europe, and in much of the developed world will live one-half their adult lives in the years after menopause, a time of relative estrogen deficiency compared to their reproductive years.

In recent years, the aging of the female population, together with the availability of “replacement” hormones, led to numerous studies of the menopause. Most of these studies were of middle-class white women living in the United States and Western Europe, with results that may not be rele-

vant to other women. In addition, many studies were clinical or epidemiological observations of associations—less satisfactory for evidence-based medicine than randomized, placebo-controlled, double-blind clinical trials. Results from recent clinical trials studying the benefits of hormone replacement therapy (HRT) have differed from observational studies. Results from additional large clinical trials, expected in the next 5 years, may further change thinking about the optimal management for the menopausal woman.

The menopause offers the health care provider an opportunity to assess each woman's health, her concerns, and the need for health promotion and disease prevention measures. Today's health care provider has to consider a bewildering array of

*From the Division of Epidemiology, Department of Family and Preventive Medicine, UCSD School of Medicine, La Jolla, California, United States.

** From the Division of Gynecology, Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Hutzel Hospital, Detroit, Michigan, United States.

***From the Division of Research, Kaiser Permanente Medical Care Program, Oakland, California, United States.

changing “facts” and sees increasingly informed patients with strong personal convictions about the menopause and their need for medication. The provider must be prepared to discuss a variety of menopause or age-related topics, and decide what to recommend for a specific woman—often in less time than ever before.

The menopause offers the health care provider an opportunity to assess each woman’s health, her concerns, and the need for health promotion and disease prevention measures.

Recommendations should be specific to each woman and her background. There are country-specific and cultural variations in menopause symptoms, the frequency of different post-menopausal diseases, clinical practice, health care resources, and afford-

able interventions. Country- and culture-specific practice will therefore vary, and appropriately so.

Recent research findings include:

- Increasing recognition of the need to address health promotion beyond the perimenopausal years, and in women with and without menopausal symptoms.
- The risks and benefits of lifestyle, pharmacological, and surgical interventions may change as women age.
- The tailoring of menopausal treatment to the individual woman should be based on her individual clinical profile and concerns.
- For the treatment of the climacteric syndrome, HRT remains the most effective pharmacologic intervention.
- The long-term benefits and risks of HRT continue to be assessed.

- HRT for long-term health promotion, as for osteoporosis, usually requires its continued use.
- New nonhormone therapies offer more options for prevention of common menopausal conditions, to be tested fully in clinical trials.
- Preventive drug therapy can start many years after menopause, particularly with respect to osteoporosis. This, however, may not be optimal.
- The risk for many disease outcomes can be reduced even in old age.

Research results are teaching us to be cautious before assuming that current practice is best. For example, although HRT remains the gold standard for the treatment of vasomotor and urogenital symptoms, as well as for the prevention of bone loss, recent clinical trial results have failed to show benefit for other menopausal conditions, such as incontinence.

Past perceptions about appropriate indications for the use of HRT were based almost entirely on clinical experience and observational data. These perceptions are being questioned as new knowledge emerges from clinical trials. Some examples follow:

Perception: HRT protects against coronary heart disease.

Evidence: The prospective randomized clinical trials reported so far have not shown benefit for reducing coronary events in secondary prevention.

The long-term benefits and risks of HRT continue to be assessed.

Perception: Estrogen prevents memory loss and retards the progression of Alzheimer’s disease.

Evidence: Clinical trials have not shown that estrogen replacement therapy retards progression of early Alzheimer’s disease. Clinical trials of the effects of estrogen replacement therapy on memory loss are still ongoing.

Perception: Estrogen improves symptoms of depression.

Evidence: Clinical trial data have shown that estrogen replacement therapy improves mood and well-being only in women with vasomotor symptoms and sleep disturbance. No convincing clinical trial data indicate that estrogen therapy in postmenopausal women is an effective treatment for major depression.

Perception: Estrogen improves urinary incontinence.

Evidence: Clinical trials have shown no benefit.

Perception: HRT, unlike oral contraceptives, does not increase the risk of venous thromboembolism.

Evidence: Clinical trials confirm a threefold increased risk of venous thromboembolism with oral estrogen replacement therapy.

Perception: HRT during the first 5–10 years after the menopause is sufficient to prevent osteoporosis in later life.

Evidence: Bone loss resumes after stopping HRT, leaving women vulnerable to osteoporosis in later life. Whether estrogen is started early or late, it must be continued into old age to maintain skeletal health.

Although many clinically relevant questions remain unanswered, women seeking advice about the menopause now have more information about and more options for healthy postmenopausal years than ever before. New trial results and new medications may further change recommendations for the assessment and management of the postmenopausal woman.

We make the following recommendations concerning HRT based on results from clinical trials. Where evidence from clinical trials is not available, we make recommendations based on observational studies. These recommendations are intended as guidelines, not mandates. All interventions should be individualized—tailored to the specific needs and concerns of each woman and designed to provide an optimal quality of life.

New nonhormone therapies offer more options for prevention of common menopausal conditions, to be tested fully in clinical trials.

2. THE MENOPAUSE TRANSITION

2.1 Assessment

Some women sail through the menopause transition with no complaints, others are miserable, and the majority have symptoms that are somewhat bothersome. There is still controversy as to which symptoms are related to menopause and which are associated with or exacerbated by other factors.

Clearly not all symptoms that occur during the menopause transition are due to hormonal changes. Only vasomotor, sleep, and some vulvovaginal symptoms have shown more favorable relief after HRT than placebo, and can therefore be convincingly attributed to changing hormone levels and menopause. At least 25 percent of women in clinical trials report significant improvement in their vasomotor symptoms when taking placebo. Therefore, convincing evidence of treatment benefit requires a placebo-controlled clinical trial.

Women may visit the physician because they have symptoms they suspect are related to menopause or because they want information about the menopause. In either case, assessment for symptoms provides an opportunity to discuss issues that might otherwise remain unaddressed.

Symptoms directly or indirectly related to the menopause transition include:

- Vasomotor symptoms (hot flushes and night sweats)
- Sleep-related symptoms
- Mood changes
- Sexual dysfunction

- Problems with concentration and memory
- Urogenital symptoms

Symptoms can be queried by using a questionnaire or symptom checklist during the interview. Some find that asking about sexual satisfaction is facilitated by the use of a checklist. When a checklist is used, it is important to go beyond the list to assess the severity and duration of reported symptoms and the degree to which they interfere with the woman's life. For example, hot flushes that are not bothersome do not require treatment.

When asking about symptoms, the clinician should be sensitive to each woman's:

- Beliefs and attitudes about menopause, including her medical vs. nonmedical treatment preferences, anxieties, and coping style
- Sociocultural and ethnic background that may affect her concerns and choices
- Work situation, job satisfaction, and stress
- Other life stressors, particularly with personal relationships
- Social supports
- Overall quality of life
- Current use of nonprescription herbal, nutraceutical (a nutritional supplement designed for a specific clinical purpose), or phytoestrogen remedies.

It is important to have a dialogue with the patient. Failure to listen and discuss may explain why many women prescribed HRT do not fill the prescription.

2.2 Symptom Prevention and Treatment. Vasomotor Symptoms: Hot Flushes and Night Sweats

2.2.1 Lifestyle

- Wear layered clothing that can be removed or added as necessary.
- There is conflicting evidence as to whether exercise improves menopause vasomotor symptoms.

2.2.2 Diet

- Avoid hot spicy foods and beverages, and reduce caffeine.
- Avoid alcohol beverages (excess can cause flushing).

2.2.3 Pharmacotherapy

- In a systematic review of more than 40 randomized controlled clinical trials, oral and transdermal estrogen each reduced the severity of vasomotor symptoms, and estrogen was effective in doses lower than the usual 0.625 mg of equine estrogens or equivalent.
- Transdermal estradiol and intranasal 17-beta estradiol spray are as effective as oral estrogen in reducing hot flushes.
- Oral tibolone is as effective as other forms of HRT such as estradiol valerate or conjugated estrogens in reducing hot flushes.
- Selective estrogen receptor modulators can increase hot flushes. In clinical trials, approximately 20 percent of women at least 2 years after menopause less than 60 years of age and 10 percent of older women developed hot flushes on raloxifene. Vasomotor symptoms were mild and rarely led to discontinuation of therapy.
- The selective serotonin reuptake inhibitors (SSRIs) venlafaxine and paroxetine have been shown to substantially reduce hot flushes in clinical trials.

- Progestogens in high daily doses (medroxyprogesterone acetate 20 mg per day or megestrol acetate 40 mg per day) also reduced vasomotor symptoms.
- Veralipride (100 mg per day) reduces hot flushes in patients treated with GnRH agonists.
- Propranolol is no more effective than placebo for the reduction of hot flushes, whereas evidence for clonidine's benefit is inconsistent.

2.2.4 Complementary and Alternative Therapies

- Phytoestrogens have not been shown in most clinical trials to decrease vasomotor symptoms significantly better than placebo. Different results may relate to differences in women (not all of them absorb phytoestrogens equally well) or differences in the products tested. The best single dietary source of phytoestrogens is soy. The U.S. Food and Drug Administration has approved a statement that soy protein at a dose of 25 gm/day may reduce the risk of CVD, based on a modest reduction in total cholesterol level.
- Dong quai has been shown in a clinical trial not to be more effective than placebo for the treatment of hot flushes.
- Evening primrose oil (gamma-linolenic acid) is not more effective than placebo for the reduction of hot flushes.

It is important to have a dialogue with the patient. Failure to listen and discuss may explain why many women prescribed HRT do not fill the prescription.

2.3 Symptom Prevention and Treatment. Urogenital Symptoms

- At least nine randomized controlled trials have shown that estrogen improves urogenital symptoms; this is true for oral and transdermal estrogen and for a silicone estradiol releasing vaginal ring. Vaginal dryness and dyspareunia can be treated with a topical estrogen cream, tablet, or vaginal ring, or with nonhormone moisturizing or lubrication products. In clinical trials, topical estrogen appears to be better than systemic

estrogen for relieving these symptoms, and avoids high levels of circulating estrogen.

- In one clinical trial, an estradiol releasing silicone vaginal ring was also found to reduce the incidence of urinary tract infection.
- Systemic estrogen alone or with a progestin does not reduce incontinence, and in one large clinical trial Heart and Estrogen/Progestin Replacement Study (HERS) actually increased incontinence.

3. FRACTURES

3.1 Assessment

When discussing osteoporosis, it is important to be sure that the provider and the patient are using the same language. Some patients confuse osteoporosis (fragile bones) with osteoarthritis (painful joints). Other women (and some doctors) mistakenly believe that a diagnosis of osteoporosis means they should not exercise.

3.1.1 Risk Factors

Many factors are associated with an increased fracture risk in women, which may differ by fracture site. Most available data are on risk factors for spine or hip fractures in Caucasian women aged 65 and older. Predicting risk in younger women and other ethnic groups is less accurate.

Nonmodifiable risk factors for fractures:

- Age—there is an approximate doubling of fracture risk every 7 years
- Family history—history of osteoporotic fracture, especially hip fracture, in either parent or sibling approximately doubles the risk
- Personal history of osteoporotic fracture increases the risk twofold to fivefold
- Early menopause increases risk

Modifiable risk factors:

- Weight—there is an increased risk if thin, and a decreased risk if overweight
- Excessive weight loss is a powerful risk factor for bone loss and fracture

- Current smoking—increases the risk of all fractures
- Low calcium intake—increases the risk of hip fracture
- Vitamin D deficiency—can cause secondary hyperparathyroidism and osteoporosis
- Inadequate physical activity
- Factors associated with falls, some of which are modifiable:
 - Limited vision
 - Impaired cognition
 - Balance problems
 - Alcohol excess
 - Poor health, frailty, muscle weakness
 - Medications, particularly sedatives
 - Environmental hazards, such as poor lighting and loose area rugs
- Low bone density is a risk factor for fracture (fracture risk doubles for every 10–12 percent decrease in bone mineral density, a deviation of approximately—1 t-score or—1 z-score (measured by dual energy x ray absorptiometry [DEXA]).

Many factors are associated with an increased fracture risk in women, which may differ by fracture site.

3.1.2 Case finding

Bone density testing is recommended in the United States for all women aged 65 years or older.

- DEXA of the hip is currently the gold standard for bone density measurements.
- Bone density results should be used in conjunction with information obtained in clinical risk assessment.

3.2 Prevention and Treatment

Better bones in old age are a function of peak bone mass (usually achieved around age 25), and subsequent rate of bone loss. Peak bone mass is maximized by an adequate calcium intake, physical activity, and not smoking. Lifestyle changes have been shown to improve bone density in young women and to prevent fractures in older women. They are low-cost, safe, and can be recommended widely.

3.2.1 Lifestyle

- Stop smoking
- Avoid extreme weight loss
- Add weight-bearing, muscle-building, and balance exercises
- Avoid sedatives
- Avoid excess alcohol
- Correct visual impairment
- Fallproof the home

Lifestyle changes have been shown to improve bone density in young women and to prevent fractures in older women.

3.2.2 Diet

- Correct calcium deficiency. A diet devoid of dairy products rarely provides more than 200 – 250 mg of calcium per day, which does not balance obligatory calcium loss and is associated with increased bone loss. Much of the bone loss can be attenuated by increasing cal-

cium intake. Ideally, the combined diet and supplement intake should be 1,200 mg of calcium each day.

- In correcting dietary calcium deficiency, the first step is to increase calcium-rich foods; each dairy portion contains approximately 300 mg. Calcium-supplemented orange juice or mineral water rich in calcium are useful for women with lactose intolerance.
- If adequate dietary calcium is not likely, calcium supplements should be recommended. Calcium supplementation should be given concomitantly with Vitamin D. Clinical trials have shown that calcium with vitamin D can reduce fracture risk; no clinical trials have shown that vitamin D without calcium significantly reduces fracture risk. Clinical trials consistently show better bone preservation in women who take calcium with estrogen than estrogen alone.
- Supplement vitamin D intake for women 65 and older; 600 – 800 IU/day together with adequate calcium intake can reduce the risk of fracture in elderly women by about 25 percent.

3.2.3 Pharmacotherapy

With growing evidence for efficacy of osteoporosis treatments and with growing concern about drug costs, policymakers have recommended that expensive drugs not be used for osteoporosis prevention. In addition, all medications have risks and side effects. Therefore, aggressive pharmacotherapy should be reserved for women who are at high risk of fracture in the near future.

Practitioners in discussion with their patients must decide between therapy with bone-specific drugs or broad-spectrum drugs (HRT, selective estrogen receptor modulators).

- Drugs shown in clinical trials to prevent bone loss, that is, to be effective in prevention of osteoporosis, include estrogen, tibolone, raloxifene, alendronate, and risedronate.

- Drugs shown in clinical trials to prevent fractures include raloxifene, alendronate, and risedronate. These clinical trials were conducted in women at increased risk of fracture. Similar large trials have not been conducted using estrogen or tibolone. HERS found no difference in clinical fracture rate or height loss (a marker for vertebral fractures) in women assigned to HRT vs. placebo. Fracture was a preset secondary endpoint in HERS, but women in this trial were not at high risk for fracture.

Estrogen therapy

- Bone loss is accelerated during the first 5–10 years following menopause, and postmenopausal estrogen therapy is effective in preserving existing bone, whether begun in old age or at the time of the menopause. Results are similar with estrogen alone or when estrogen is used with a nonandrogenic progestin such as medroxyprogesterone acetate or progesterone. Androgenic progestins such as norethisterone-acetate have a synergistic activity when combined with 17-beta estradiol.
- Clinical trials have shown that doses of 0.3 mg per day of conjugated equine estrogen (lower than the previously recommended 0.625 mg per day), 0.5 mg of oral 17-beta estradiol or 25 micrograms of transdermal 17-beta estradiol maintain bone in most women when taken with adequate calcium. Smaller doses were better tolerated with regard to fewer episodes of uterine bleeding and less breast tenderness, two major reasons why women discontinue estrogen. Whether lower dosages of estrogen will be safer (lower rates of venous thromboembolism, breast cancer) remains to be proven.

When medication is indicated, based on a combination of clinical risk factors and low bone mineral density, the choice varies with the age of the patient and the severity of osteoporosis.

- Estrogen must be used continuously to preserve bone. Observational data suggest that bone density in older women who have never received estrogen is similar to bone density in women who used estrogen for 10 years and then discontinued it for another 10 years.
- Hormone treatment of women soon after menopause should be reserved for management of postmenopausal symptoms, but it will preserve bone in most women.

Non-estrogen therapy

Asymptomatic women 10 or more years postmenopause, without severe osteoporosis, may prefer tibolone or raloxifene. For women aged 60 or older who have osteoporosis but are not at high risk for nonspine fracture, raloxifene can be used to reduce the risk of spine fractures and for its possible other health benefits. Older women, particularly those with severe osteoporosis and prior fracture(s), may prefer alendronate or risedronate for their rapid acting bone-specific effects and reductions in nonspine as well as spine fractures.

Parathyroid hormone treatment by daily injection promises to be particularly effective for women with very severe osteoporosis who need to gain substantial amounts of bone.

The way medications are prescribed influences patient adherence. Beginning with a low dose for women prescribed estrogen helps reduce breast pain and slowly increasing dosage of raloxifene is useful in overcoming the hot flush side effect. Women who cannot tolerate the first medication often tolerate one of the other bone-sparing medications. A few trials have shown improved bone density over single therapy when a bisphosphonate is combined with estrogen or raloxifene, but there

Aggressive pharmacotherapy should be reserved for women who are at high risk of fracture in the near future.

are no fracture data in women using these combinations (and the cost of combination therapy precludes routine use).

- Statins have been inconsistently associated with higher bone density. Statins have not been consistent in reducing bone loss or fracture risk, and these skeletal benefits have not been assessed in clinical trials.
- Clinical trial data show that a thiazide diuretic reduces but does not prevent bone loss.
- Observational studies suggest that people using thiazides are less likely to have fractures.

3.2.4 Complementary and Alternative Therapies

- Soy food (soy protein isolate) has been shown in clinical trials to have little or no benefit for the skeleton when ingested in the usually recommended amounts (20 – 25 grams of soy protein per day).
- Ipriflavone, a synthetic isoflavone, has been shown in preliminary studies to reduce bone loss but failed to improve bone density or reduce fracture risk in a large clinical study of women with osteoporosis.

4. CARDIOVASCULAR DISEASE

4.1 Assessment

When assessing a woman's knowledge about heart disease and stroke prevention, it is important to note that cardiovascular disease (CVD) is a more common cause of morbidity and mortality for women in most of the world than osteoporosis and cancer combined.

CVD is a more common cause of morbidity and mortality for women in most of the world than osteoporosis and cancer combined.

4.1.1 Risk Factors

The main risk factors for coronary heart disease (CHD) are: high blood cholesterol, high blood pressure, diabetes, and cigarette smoking. These same factors also apply to stroke and peripheral arterial disease, but the order of importance differs. High blood pressure is the most important risk factor for stroke, while

smoking has been consistently associated with peripheral arterial disease, and high blood cholesterol with CHD.

Nonmodifiable risk factors

- Age. For every 10-year increase in age, the risk for heart disease increases about threefold.
- The presence of CHD or other evidence of atherosclerotic arterial disease including stroke or lower extremity arterial disease increases the risk for myocardial infarction (MI) about fivefold. Atrial fibrillation, aortic stenosis, and narrowing of the coronary arteries are also risk factors for stroke.

- Family history of premature CHD (MI before age 55 in men, 65 in women) increases the risk for MI about twofold.
- The importance of a positive family history is amplified in women who smoke cigarettes.

Modifiable risk factors

- Cigarette smoking: Compared to smokers, nonsmokers or women who stop smoking have one-third the risk for MI.
- Physical activity: Women who walk briskly for 3 hours per week have a one-third lower risk for MI compared to women who do little exercise.
- Nutrition: Women whose usual diet is low in saturated and trans fats, and relatively high in unsaturated fats (including monounsaturated fats and fish oils), and high in cereal fiber, fruits, and vegetables, have half the risk for MI compared to women who do not have this healthy eating pattern.
- Weight: Lean women (body mass index below 25) have one-quarter less risk than overweight women, and less than one-half the risk of obese women (body mass index above 30).
- Fat distribution: Women with a waist circumference of less than 28 inches (71 cm) have one-third the risk for MI compared to women with a waist circumference of more than 38 inches (96.5 cm). Weight and weight distribution associated risks are not the same in all populations. For example, overweight and central obesity seem to be less important risk factors in African American women than in women of northern

European ancestry and Asian American women who seem to be at increased risk at lower weights.

- Psychosocial factors: Life stress situations, depression, and social isolation have been linked to increased risk for MI in women.
- Blood pressure: Women with a systolic blood pressure below 140 mmHg have a risk for MI one-half that of women with a level above 180 mmHg.
- Blood cholesterol: Women with a LDL cholesterol below 130 mg/dL (3.4 mmol/L) have a risk for MI one-half that of women with levels above 190 mg/dL (4.9 mmol/L).
- HDL cholesterol: Women with a HDL cholesterol level above 60 mg/dL (1.6 mmol/L) have a risk for MI which is one-third that of women with a level of less than 40 mg/dL (1.0 mmol/L). Contrary to popular opinion, women with high HDL cholesterol levels are not immune to MI.
- Triglycerides: Women with triglyceride levels below 150 mg/dL (1.7 mmol/L) have a risk of MI one-third lower than women with levels above 240 mg/dL (2.7 mmol/L).

The main risk factors for CHD are: high blood cholesterol, high blood pressure, diabetes, and cigarette smoking...

without diabetes. About half of women with Type 2 diabetes do not know they have it. Diabetes is often first diagnosed when the patient has a MI.

- Diabetes: Women with diabetes by history or glycemia (fasting plasma glucose > 126 mg/dL (7.0 mmol/L) and/or 2 hour postchallenge glucose above 199 mg/dL (11.1 mmol/L) have a two- to fourfold increased risk of MI compared to women

4.1.2 Other Assessments

History

- Presence of any of the risk factors above.
- Symptoms compatible with transient ischemic attack, CHD, or lower extremity atherosclerosis.
- Use of HRT, antihypertensive drugs, lipid-lowering therapy, aspirin, and medication for diabetes.

Physical examination

- Pulses, auscultation for cardiac murmurs, and arterial bruits.
- Blood pressure at first visit. Women who have optimal blood pressure levels (<130/85 mmHg) are rechecked every 2 years (Europe: women > 40 years: every year), those with normal levels (<140/90 mmHg) are rechecked every year. Women with levels >140/90 mmHg need confirmation.
- Height, weight, waist circumference, calculate body mass index (BMI).

Laboratory tests

- Fasting glucose, total cholesterol, HDL cholesterol, triglycerides, calculated LDL cholesterol at first visit. For women without known CHD, the desirable lipid levels are LDL cholesterol <130 mg/dL (3.4 mmol/L), triglycerides <150 mg/dL (1.7 mmol/L), and HDL cholesterol levels >45 mg/dL (1.3 mmol/L).
- Repeat measurements that are normal every 5 years.
- Evidence does not support further screening for diabetes. Case finding may be appropriate in persons who have central obesity, high triglycerides, or a positive family history. Repeat glucose tests for women whose fasting blood glucose is elevated because the diagnosis of diabetes needs a confirmatory test. Women whose fasting plasma glucose is between 110 (6.1 mmol/L) and 126 mg/dL (7.0 mmol/L) or whose 2 hour glucose is between 140 (7.8 mmol/L) and 200 mg/dL (11.1 mmol/L) are at high risk of future diabetes.

- In some countries, homocysteine measurement is recommended.

Women with diabetes ... have a two- to fourfold increased risk of MI ...

Other tests for CHD, cerebral arterial disease, and peripheral vascular disease as indicated by symptoms.

The combined effect of two or more risk factors is more powerful than any single risk factor, and some risk factors commonly occur together.

(For example, screening for

diabetes may be most appropriate in persons with high blood pressure or high triglyceride levels.)

When one risk factor is found, the presence of other factors should be sought and an assessment of overall risk should be made by counting the number of risk factors plus a 10-year risk assessment as in the National Cholesterol Education Program's Adult Treatment Panel III Report (NCEP ATP III) or as an assessment of the 10-year risk as recommended in European guidelines. Risk assessment can be used to motivate the patient to make lifestyle changes and comply with medication.

4.2 Prevention and Treatment

Even in the absence of clinical trial data, lifestyle and diet recommendations can be made to all women, not just those with heart disease risk factors or disease, because the diet, physical activity, and not smoking recommendations represent a return toward the evolutionary norm.

4.2.1 Lifestyle

- At each visit, reinforce nonsmoking status, or strongly encourage patient (and family) to stop smoking and avoid secondhand smoke. Prescribe counseling, nicotine replacement, or other pharmacotherapy as indicated in conjunction with behavioral therapy or a formal smoking cessation program.

- Encourage a minimum of 30 minutes of moderate-intensity dynamic exercise, e.g., brisk walking, at least 3 days a week, supplemented by an increase in daily lifestyle activities. Women who want to do more than the minimum should be encouraged to do so. Recommend medically supervised programs for women who have had a recent MI or revascularization procedure.
- Encourage gradual weight loss for overweight women through a combination of physical activity and portion control, healthy food choices, and recognition of triggers to overeating. Refer to weight loss support group or formal nutritional counseling when appropriate.
- Encourage positive coping mechanisms for stress (e.g., substitute physical activity for overeating or smoking in response to stressful life situations).

4.2.2 Diet

- Encourage a well-balanced and diversified eating pattern that is low in saturated fat and high in fresh fruits and vegetables and fiber. Prefer fats with higher monounsaturated content (e.g., olive oil, canola oil). Prefer seafood and skinless chicken to red meat. Prefer soft unsaturated margarine to hard margarine or butter. Use skim milk and skim milk products or at most 1 percent milk instead of products with a higher fat content. Limit the intake of high-cholesterol foods, avoid fast-food meals. Consume more than five servings of fruits and vegetables daily. Total dietary fiber intake from food should be 25–30 g per day.
- A clinical trial showed that eating fish two to three times per week reduced the risk of CVD.
- Encourage increased dietary consumption of omega-3 fatty acids.
- A clinical trial showed that a “Mediterranean diet,” supplemented with alpha-linoleic acid, significantly reduced the risk of recurrent coronary events in patients with heart disease.

- Diets rich in antioxidant vitamins (i.e., nuts, fruits, and vegetables) are preferred over vitamin supplements.
- Limit salt intake to 6 g per day. A reduced salt/reduced saturated fat diet has been shown to reduce blood pressure in clinical trials.

Even in the absence of clinical trial data, lifestyle and diet recommendations can be made to all women ...

- Prefer spices to salt in food preparation. Reduce intake of canned and commercial bakery goods, which are usually high in salt.
- Limit alcohol to less than one to two glasses per day: one glass equals 4 ounces of wine (approx. 120 mL),

12 ounces of beer (approx. 360 mL), or 1 1/2 ounces of 80-proof spirits (approx. 45 mL).

4.2.3 Pharmacotherapy

Blood pressure

- Achieve and maintain blood pressure <140/90 mmHg or lower if tolerated. If blood pressure remains above 140/90 mmHg after 3 months of reduced dietary salt, saturated fats and attempted weight loss, or if initial level is above 160/100 mmHg, initiate individualized pharmacotherapy. Goal blood pressure <130/80 mmHg if diabetic.

Beta-blockers, low-dose diuretics, and angiotensin converting enzyme (ACE) inhibitors have been shown in clinical trials to reduce the risk of MI in patients with high blood pressure.

Lipids and lipoproteins

- LDL cholesterol
 - (a) In women without CHD or CHD risk equivalents (other forms of atherosclerotic disease, diabetes, or 10-year risk more than 20 percent), the desirable LDL cholesterol level is <130 mg/dL (3.4 mmol/L).

- If the LDL cholesterol level is >130 mg/dL (3.4 mmol/L) and two or more other risk factors are present, or the 10-year risk of MI is more than 10 percent, implement intensive lifestyle intervention and consider pharmacotherapy. If the 10-year risk is less than 10 percent, consider pharmacotherapy if the LDL cholesterol is >160 mg/dL (4.1 mmol/L).
- If the LDL cholesterol level is >190 mg/dL (4.9 mmol/L), pharmacotherapy is usually required.

(b) In women with CHD or CHD equivalents, the desirable LDL cholesterol level is 100 mg/dL (2.6 mmol/L) or lower, and pharmacotherapy is generally required.

- Triglycerides and HDL cholesterol
 - If the triglycerides are >150 mg/dL (1.7 mmol/L) and the HDL cholesterol is below 40 mg/dL (1.0 mmol/L), treatment should still be aimed primarily at the LDL level. Lowering triglycerides and raising HDL levels become secondary targets of therapy and may influence the choice of drugs. Women with elevated triglycerides as their only lipid abnormality usually respond to intensive lifestyle measures. Some patients with very high triglyceride levels respond best to fibrates or niacin.
- Choice of drugs
 - Statins are the drugs of choice for high LDL cholesterol levels, irrespective of the levels of triglycerides or HDL cholesterol. Statins have been shown in clinical trials to reduce the risk of MI and stroke.

For women with moderate elevations of LDL cholesterol, raised triglycerides, and low HDL cholesterol levels, statins are the first choice. Fibrates and niacin have not been shown in randomized clinical trials (RCTs) to reduce CHD risk in women, although recommended

in AHA/ACC (American Heart Association/American College of Cardiology) guidelines for low HDL or high triglycerides. Start statin therapy promptly in patients with acute coronary syndrome.

HRT given orally reduces LDL cholesterol by 10 percent, raises HDL cholesterol by 10 percent, and raises triglycerides by 20 percent. HRT is not recommended for management of lipid disorders because of the lack of clinical trial evidence showing cardiovascular benefit.

Diabetes

- Target preprandial blood glucose in the range of 80–120 mg/dL (4.4–6.7 mmol/L), bedtime 100–140 mg/dL (5.5–7.8 mmol/L), Hgb A1c <7 percent
- Maintain LDL cholesterol <100 mg/dL (2.6 mmol/L) and triglycerides <150 mg/dL (1.7 mmol/L)
- Maintain blood pressure <130/80 mmHg (optimal <120/75 mmHg)
- In clinical trials, the initiation of oral HRT is accompanied by a two- to fourfold increased risk of venous thromboembolism and a small early increased risk of CHD and stroke. Based on observational studies, a reduction in risk for CHD after 2 or more years is possible, but the clinical trial evidence is lacking. Some experts see no reason to discontinue HRT in women who have been treated for many years, in view of the expected benefit for osteoporosis. Based on clinical trial data, an increased risk of venous thromboembolic disease persists for at least 4 years. The absolute increase in risk for venous thromboembolism is small—approximately two excess events in 8,000 treated women. This risk

may be reduced in women taking aspirin or statins.

- A history of venous thromboembolic disease is a contraindication to HRT.
- Low-dose aspirin can be recommended for women with established CVD (based on clinical trial data and probably for high-risk women [by inference only]). There is some concern that the risk benefit ratio may be different in women, who seem to have a higher risk of stroke than men. Consider clopidogrel or warfarin if aspirin contraindicated.
- Beta-blockers: If there are no contraindications (e.g., severe bradycardia, high degree heart block, acute heart failure, asthma, active peripheral vascular disease) start betablockers within hours of hospitalization for MI and acute coronary syndromes, or as soon as possible thereafter to lower the risk of reinfarction and of cardiac failure.
- ACE inhibitors. If there are no contraindications (e.g., renal artery stenosis, aortic stenosis, or severe hypotension), start ACE inhibitors within hours of hospitalization for MI, or as soon as possible thereafter, to lower the risk of reinfarction and of cardiac failure. Use ACE inhibitors to lower the risk of MI and death in patients with cardiac failure, left ventricular dysfunction, or high risk for CHD.

4.2.4 Complementary and Alternative Therapies

- Trials of vitamin E and beta-carotene supplements have failed to show benefit for CVD prevention.

5. CANCERS (BREAST, CERVIX, COLORECTAL, ENDOMETRIAL, OVARY, AND LUNG)

The major cancers that occur in postmenopausal women are breast, cervix, colorectal, endometrial, ovary, and lung.

In observational studies, the increased risk of breast cancer after 5 or more years of estrogen replacement therapy is similar to the risk associated with a delayed menopause or with obesity. In some of these studies, breast cancer risk was higher in women who used estrogen plus a progestin and higher in women who used estrogen plus progestin cyclically.

In observational studies, the increased risk of breast cancer after 5 or more years of estrogen replacement therapy is similar to the risk associated with a delayed menopause or with obesity.

Endometrial cancer is associated with endogenous or unopposed exogenous estrogen levels. An increased risk of endometrial cancer occurs in menopausal women who have low levels of progestin to counterbalance the stimulating effect of estrogen on the endometrium. A 3-year clinical trial has shown that endometrial hyperplasia, a uterine cancer precursor, occurs in 10 percent of women for each year of unopposed estrogen use.

A number of observational epidemiological studies (including both prospective and case-control studies) have consistently shown that women on HRT have

reduced risks of developing colorectal cancer or adenoma and of dying from colorectal cancer. There is weak evidence from observational studies that HRT increases the risk of ovarian and lung cancer.

Much of the increased risk for cancers in postmenopausal women can be linked to the effects of age and accumulated lifetime exposure to carcinogens.

5.1 Assessment

5.1.1 Risk Factors

Nonmodifiable risk factors

- Family history of breast, ovarian, or colorectal cancer, especially in a first degree relative.
- Age. Most cancer rates increase with age. The year-by-year increase in breast cancer rates persists but is less steep in women who do not take estrogen after the menopause.
- Previous history of cancer (invasive and in situ).
- Precursor lesions (benign proliferative breast disease, colorectal polyps, endometrial hyperplasia, and high grade squamous intra-epithelial lesions of the cervix infected with selected variants of human papillomavirus[HPV]).
- Reproductive and menstrual factors: Early menarche and late menopause increase risk for breast cancer, and possibly also endometrial and ovarian cancer. Early first pregnancy and multiparity decrease the risk for breast and ovarian cancers. Multiparity also reduces the risk of endometrial cancer.

Modifiable risk factors

- Estrogen treatment: Excess exogenous estrogen in the postmenopausal years increases risk for breast and endometrial cancers. It is unknown whether lower doses of estrogen will have different risks and benefits. Use of a progestin with the estrogen may increase breast cancer risk, but it decreases endometrial cancer risk if taken in an adequate regimen, either 10–14 days per month or daily. Past oral contraceptive use greater than 1 year decreases endometrial and ovarian cancer risk.
- Overweight: Heavier postmenopausal women are at increased risk for cancer of the breast, endometrium, and colon. The risk for breast cancer in obese women is comparable to that for long-term HRT.
- Nutrition: Women whose usual diet is low in fat and high in vegetables, fruits, and fiber have a reduced risk for colorectal and breast cancer. Recent clinical trials found no reduced risk of colon polyps, a cancer precursor, after either a high-fiber diet or a diet enriched with fruits and vegetables.
- Physical activity: Physically active women may have a reduced risk for colon cancer and possibly also breast and endometrial cancer.
- Cigarette smoking: Women smokers are at increased risk for lung, cervix, colorectal, oral, esophageal, and pancreatic cancers, as well as other less common epithelial cell cancers.
- Alcohol: Alcohol use increases the risk for breast (probably by increasing endogenous estrogen levels) and colon cancer, as well as more rare head and neck cancers.
- Radiation: High doses of radiation, used in the past for certain medical treatments, have been associated with increased risk for several cancers.

- Other exposures: Women infected with specific strains of HPV are at increased risk for cervical cancer.
- High radiographic density on mammogram carries about a twofold increased risk for breast cancer and may delay diagnosis by making mammograms harder to read. A clinical trial showed that this reversible condition occurs within 1 year in about 15 percent of most postmenopausal women treated with estrogen alone and in more than one-third of those treated with estrogen plus a progestin.

Much of the increased risk for cancers in postmenopausal women can be linked to the effects of age and accumulated lifetime exposure to carcinogens.

5.1.2 Case-finding

History

- Presence of any of the risk factors above

Physical examination

- Height, weight
- Clinical breast exam
- Pelvic exam
- Colorectal screening (can include fecal occult blood assay, flexible sigmoidoscopy, and colonoscopy).

Specific tests

The selection of screening modality and frequency will depend on individual and population prevalence of disease and available resources.^a

^aHorton R. Screening mammography—an overview revisited. *Lancet* 2001;358:1284–1285.

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- Mammograms: There is disagreement about the benefit of mammograms before age 50, but women taking HRT and those with other risk factors may want to be tested. Mammograms are usually performed annually or biannually.

Despite much interest in complementary and alternative therapies, there are no trial data on their efficacy in reducing cancer risk.

Because women's risk of breast cancer continues to increase with age, regular mammography screening remains appropriate even in old age although the benefit in women over age 75 has not been tested.

- Cervical smears: In countries where cervical cancer rates increase with age, cervical smears should be continued into old age.
- Pap smears have poor positive predictive value for postmenopausal women and do not have to be performed more often than every 2–3 years after a normal cytological result. The main advantage of an annual Pap smear is that it increases overall adherence to regular examination. Clinical observation shows no effect of hormone replacement therapy on cytologic abnormalities.
- Special methods that include testing for carcinogenic HPV strains reduce the number of false-positive results and the attendant anxiety and cost. In the future, these tests may replace the Pap smear as the gold standard for early detection of cervical cancer.

5.2 Prevention and Treatment

Despite a great deal of information on factors that increase cancer risk, there are limited data on what can be done to reduce risk. There have been few clinical trials of prevention modalities. It is not clear that reversing a risk factor will reduce cancer risk. Nevertheless, some practical recommendations can be made.

5.2.1 Lifestyle

- Stop smoking.
- Limit alcohol use to less than one to two glasses per day: 1 glass equals 4 ounces of wine (approx. 120 mL), 12 ounces of beer (approx. 360 mL), or 1 1/2 ounces of 80-proof spirits (approx. 45 mL).
- Avoid unnecessary radiation.
- Avoid unopposed estrogen replacement therapy if uterus is present.
- Avoid HRT for more than 5 years except in presence of specific indications.
- Avoid postmenopausal weight gain.
- If overweight or obese, lose weight.
- Increase physical activity.

5.2.2 Diet

- Increase intake of vegetables, fruits, and fiber.
- Decrease fat and red meat intake.

5.2.3 Pharmacotherapy

Breast Cancer

- Consider tamoxifen use if high risk for breast cancer; a North American clinical trial found a reduced risk for breast cancer with 5-year use. Tamoxifen increases the risk of endometrial cancer, venous thromboembolism, and vasomotor symptoms.
- Although raloxifene is not approved for prevention or treatment of breast cancer, a 4-year trial of raloxifene in women with osteoporosis (not at high risk for breast cancer) showed a 90 percent risk reduction for estrogen-receptor positive breast cancer, and no increased risk of uterine cancer. Breast density is not increased with raloxifene use. A trial comparing raloxifene with tamoxifen is underway.

- When prescribing estrogen to women with an intact uterus, prescribe at least 10–14 days per month of progestin, to reduce endometrial cancer risk.
- Do not give progestin to women without a uterus; it is not necessary, and some observational studies suggest that estrogen plus progestin increases the risk of breast cancer more than estrogen alone.

5.2.4 Complementary and Alternative Therapies

- Despite much interest in complementary and alternative therapies, there are no trial data on their efficacy in reducing cancer risk. The most attractive candidate is soy protein, based on observational studies of low breast cancer risk in countries with high soy intake.
- A trial of the effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas, a cancer precursor, failed to show the benefit of such a diet in reducing risk.

Other: Very-High-Risk Patients

- Consider removal of at-risk organs.
- Very high risk for breast cancer: additional screening by sonography.
- There is no trial evidence that additional screening such as pelvic ultrasound or Ca125 for women at high risk for ovarian cancer or beginning mammography before age 40 for women at high risk for breast cancer will improve the prognosis.
- Colonoscopy for women at high risk for colorectal cancer can be recommended based on clinical trial data.

6. DEMENTIA AND MENTAL HEALTH

For most disorders affecting the central nervous system, there are inadequate data upon which to base practice decisions. Alzheimer's disease merits particular mention, because it is common and a major concern of older women.

6.1 Assessment

6.1.1 Risk Factors for Alzheimer's Disease

- The only consistently identified risk factors are age, family history, and apolipoprotein E e4 allele.

For most disorders affecting the central nervous system, there are inadequate data upon which to base practice decisions.

- The risk of developing Alzheimer's disease doubles approximately every 5 years through the ninth decade of life.
- Uncommon forms of the illness that appear before the seventh decade of life are often transmitted as autosomal dominant disorders.
- Dominant inheritance is not characteristic of later-onset dementia, although family history remains a risk factor in this age group.
- Some observational studies suggest other risk factors for Alzheimer's disease, including prior history of head trauma, low educational achievement, presence of CHD, hypertension or hyperlipidemia, prior history of depression, and the absence of HRT. The evidence for these associations is inconsistent.

- Polypharmacy and thyroid disease are two examples of reversible causes of memory loss in older adults.
- Depressed mood is fairly common in persons with dementia; it may impair cognitive function or be a consequence of it.

6.1.2 Case-Finding for Suspected Dementia

- The medical, neurological, and psychiatric history should focus on potential causes of cognitive and behavioral change, including stroke, endocrine disease (e.g., thyroid disorders), toxic exposures (particularly the excessive use of psychotropic medications or medications with psychotropic side-effects), and depression.
- Family history should be assessed.
- Functional decline should be documented.
- The mental status examination should evaluate both cognition and mood. Commonly used tests for cognitive function are the Mini-Mental State Examination (MMSE) and the short Blessed Test for Orientation-Memory-Concentration. Standard validated questionnaires are available for testing for depressed mood in the elderly (e.g., the Beck Depression Inventory and the Geriatric Depression Scale).
- Laboratory assessment in the patient with dementia usually includes complete blood count; serum electrolytes and glucose; tests of renal, liver, and thyroid function; and B-12 level. Screening for syphilis and HIV should be considered in at-risk populations.

- Brain imaging study (CT scan or MRI scan) is often used to exclude space-occupying lesions, evaluate suspected cerebrovascular disease, or evaluate suspected hydrocephalus. The diagnostic yield for this procedure is low if the neurological examination is normal and the history and examination are otherwise typical for Alzheimer's disease.
- A common cause of cognitive impairment in the elderly is overmedication. A careful review of all medications taken by the patient may lead to the identification of a reversible cause of confusion or memory loss.

6.2 Prevention and treatment

- There are no proven preventive measures for Alzheimer's disease. For prevention of vascular dementia, it is reasonable to follow preventive recommendations listed for CVD.

6.2.1 Lifestyle

- Ensure a safe, stable, and structured environment.
- Encourage social interventions such as power of attorney and caregiver respite as appropriate.

6.2.2 Diet

- Diet should be well-balanced.
- Discourage excess alcohol use.
- Discourage smoking, which can pose a fire hazard.

6.2.3 Pharmacotherapy

- Reduce unnecessary or optional medications.
- Identify and treat depression and other behavioral disturbances when they are distressing to patients or hinder their care.
- There is clinical trial evidence that drugs that inhibit the breakdown of acetylcholine in the brain are often of mild symptomatic benefit.
- There is no clinical trial evidence that estrogen improves symptoms or delays symptomatic progression in women with Alzheimer's disease.
- There are no published long-term clinical trial data on potential effects of HRT on age-associated cognitive decline.
- One clinical trial found that vitamin E slows progression without improving cognition in patients with moderate dementia due to Alzheimer's Disease.
- One clinical trial of antihypertensive medication in cognitively intact older adults with hypertension showed a small but significant difference in the rate of memory loss and the incidence of dementia in those on active treatment.
- One clinical trial found raloxifene was associated with less cognitive decline in two cognitive function tests in older women.

6.2.4 Complementary and Alternative Therapies

- There is limited trial evidence that ginkgo biloba may offer mild cognitive benefit when given to patients with dementia.

7. CONCLUSIONS

In the last 20 years, menopause has become a household word, with much better understanding of its consequences. The growing numbers of postmenopausal women and clinical trials have coincided to draw increasing attention to the perimenopausal and postmenopausal years. Better

studies of older therapies and the expanded number of new choices today, with more in development and evaluation, have complicated provider and patient choices, but greatly improved the potential for effective intervention.

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